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Research Progress on Anthracycline-Induced Cardiotoxicity in Breast Cancer Patients

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Abstract: ***Anthracycline chemotherapeutic agents, including doxorubicin, epirubicin, and pirarubicin, are widely utilized in the treatment of various malignancies. These agents demonstrate significant efficacy against hematological tumors (e.g., Hodgkin lymphoma, non-Hodgkin lymphoma, and pediatric leukemia) and solid tumors (e.g., ovarian cancer, breast cancer, and gastrointestinal malignancies), playing a pivotal role in breast cancer management. However, prolonged use of these agents is associated with multiple adverse effects, including allergic reactions, cardiac damage, alopecia, myelosuppression, emesis, and bladder irritation. The most severe complication is doxorubicin-induced cardiomyopathy, which compromises myocardial function, reduces left ventricular ejection fraction (LVEF), and may lead to congestive heart failure. Although anthracycline-induced cardiotoxicity is dose-dependent, it may manifest early during treatment or emerge years after therapy cessation. The precise mechanisms underlying doxorubicin-induced cardiotoxicity remain incompletely elucidated. This review synthesizes recent research on anthracycline-induced cardiotoxicity in breast cancer patients, encompassing classification, pathogenesis, and current prevention and treatment strategies, aiming to provide references for early clinical monitoring, diagnosis, and management of this condition.***

Keywords: Anthracyclines, Cardiotoxicity, Breast cancer.

1. Introduction

Breast cancer (BC) represents the most prevalent malignant tumor among women globally. According to the 2024 Global Cancer Statistics Report, breast cancer accounts for 32% of newly diagnosed cancer cases in women, ranking first in incidence [1], posing a substantial threat to women's health and well-being. While advancements in targeted therapies and immunotherapeutics have significantly reduced breast cancer mortality, the associated cardiotoxicity of anticancer agents has emerged as a critical concern [2].

Comprehending the cardiotoxic profiles of contemporary breast cancer treatments and appropriately managing cardiovascular risk factors are essential for mitigating cardiotoxicity risks. The adverse cardiovascular effects of antitumor drugs, including vasospasm, arrhythmia, left ventricular dysfunction (LVD), and heart failure (HF), are particularly pronounced in elderly patients and those with comorbidities [3]. Anthracyclines, such as doxorubicin (DOX), epirubicin, and pirarubicin, remain cornerstone agents in breast cancer chemotherapy, with their toxicities being extensively studied [4]. Anthracycline-induced cardiotoxicity is typically progressive and irreversible, with most cases occurring within the first year of chemotherapy and correlating with cumulative anthracycline dose and post-treatment LVEF [5]. Therefore, early detection and timely intervention are crucial for optimal cardiac function recovery.

2. The Definition of Anthracycline-Induced Cardiotoxicity

The diagnostic criteria for chemotherapy-induced myocardial injury in breast cancer patients remain inconsistent. The 2013 Guidelines for Prevention and Treatment of Anthracycline Cardiotoxicity define drug-induced cardiotoxicity as myocardial lesions resulting from direct myocardial exposure and/or systemic toxic effects of certain drugs, manifesting as arrhythmias, abnormal cardiac contractile/diastolic function, myocardial hypertrophy, or cardiac enlargement. The definition of antitumor drug cardiotoxicity encompasses subclinical cardiovascular injury occurring early during chemotherapy/targeted therapy: (1) LVEF reduction cardiomyopathy, characterized by global functional decline or significant ventricular septal motion impairment; (2) symptoms of congestive heart failure (CHF); (3) CHF-related signs, such as S3 gallop rhythm and tachycardia; (4) LVEF reduction ≥5% from baseline to <55% with CHF symptoms/signs, or LVEF reduction ≥10% to <55% without symptoms/signs [6].

3. The Classification of Anthracycline Cardiotoxicity

Anthracycline cardiotoxicity can be categorized into acute, chronic, and late-onset forms. Acute cardiotoxicity occurs within hours or days post-administration, typically presenting as conduction abnormalities and arrhythmias, with rare cases of pericarditis and acute left heart failure [3]. Chronic cardiotoxicity develops within one year post-treatment, manifesting as left ventricular dysfunction progressing to heart failure [7]. Late-onset cardiotoxicity emerges several years after treatment, potentially presenting as heart failure, cardiomyopathy, and arrhythmias [7,8]. A retrospective analysis of 149 sarcoma patients [9] revealed that cardiotoxicity is relatively common in doxorubicin-treated patients, with baseline diastolic blood pressure significantly associated with cardiotoxicity risk.

4. The Mechanisms of Anthracycline-Induced Cardiotoxicity

4.1 Oxidative Stress

Anthracyclines exhibit high affinity for mitochondrial

phospholipids and cardiolipin, accumulating preferentially in mitochondria-rich cardiomyocytes. Oxidative stress arises from an imbalance between reactive oxygen species (ROS) generation and endogenous antioxidant activation, resulting in myocardial toxicity. Elevated ROS production and diminished antioxidant factors (e.g., superoxide dismutase [SOD], glutathione [GSH], catalase [CAT]) are associated with doxorubicin-induced cardiomyopathy. Oxidative stress and lipid peroxidation can induce cellular damage, apoptosis, cardiomyocyte death, and ultimately heart failure [10,11].

In doxorubicin-related cardiotoxicity, oxidative damage increases malondialdehyde (MDA) levels [12], markers of oxidation and peroxidation processes. Excessive ROS production induces lipid peroxidation and accumulation of reactive electrophiles (e.g., 4-HNE, a DOX-induced oxidative stress biomarker) [13]. Furthermore, doxorubicin administration triggers excess ROS production and ROS-mediated nuclear p53 activation, leading to mitochondrial damage, including mitochondrial DNA mutations, membrane permeability disruption, and calcium ion homeostasis impairment [14,15]. Nuclear factor erythroid 2-related factor 2 (Nrf2), a redox-sensitive transcription factor, regulates detoxification and cellular responses to oxidative stress, upregulating antioxidant genes such as heme oxygenase-1 (HO-1) [16]. HO-1 activity inhibits inflammation, apoptosis, and oxidative stress [17], while Nrf2 pathway inhibition following doxorubicin administration is associated with cardioprotective enzymes mitigating DOX-induced oxidative damage [18]. The Nrf2/HO-1 signaling pathway has been extensively studied in DOX cardiotoxicity research.

4.2 Inflammatory Pathways

Doxorubicin-induced cardiotoxicity involves cardiac inflammation, stimulating inflammatory cytokine production, enhancing natural killer (NK) cell activity, and activating cytotoxic T lymphocyte (CTL) responses [19,20]. Inflammation-related signaling pathways play crucial roles in DOX-induced cardiotoxicity. DOX-induced inflammatory cytokine production and oxidative stress activate NF-κB, a major inflammatory transcriptional regulator, in cardiomyocytes. DOX converts the IκB/NF-κB complex into active NF-κB, inducing inflammatory cytokines (e.g., TNF-α, IL-1β) that exhibit cardiotoxic effects through other inflammatory pathways [10,11]. Recent studies demonstrate that enoxaparin treatment significantly reduces cardiac TNF-α and IL-1β levels, suggesting cellular protection against DOX-induced cardiotoxicity in rat models through NF-κB pathway inactivation and subsequent cytokine release inhibition [21]. DOX increases proinflammatory cytokines while decreasing IL-10, an anti-inflammatory cytokine. IL-6 and TNF-α are valuable predictors of DOX-induced cardiovascular disease incidence and mortality. Cardiac myocytes and endothelial cells produce IL-6, with myocardial IL-6 expression correlating with DOX-induced cardiotoxicity progression. DOX administration elevates cardiac nitric oxide (NO) levels, potentially through increased inducible nitric oxide synthase (iNOS) expression, a pathway possibly influenced by NF-κB activation [22]. Studies indicate that reduced IL-1β, IL-6, and TNF-α levels are associated with MAPK/NF-κB pathway inhibition, with exogenous H2S ameliorating DOX-induced inflammation and cytotoxicity [23].

4.3 Mitochondrial Damage

Cardiomyocytes possess higher mitochondrial numbers than other tissues, crucial for ATP production. Mitochondrial damage represents a key mechanism of DOX-induced cardiotoxicity. DOX treatment increases ROS production, disrupting mitochondrial ATP synthesis. Additionally, cardiolipin forms stable complexes with DOX, enhancing mitochondrial ROS generation [24]. DOX can induce mitochondrial DNA (mtDNA) mutations and defects, accompanied by increased mitochondrial ROS, both contributing to cardiomyopathy development. DOX-induced nuclear damage may inhibit SIRT3 expression, with reduced SIRT3 concentrations leading to excessive ROS production, mitochondrial dysfunction exacerbation, mtDNA damage, cellular injury, and heart failure [25]. Consequently, numerous studies focus on mitigating mitochondrial damage to reduce DOX-induced cardiotoxicity. Derezosen effectively prevents DOX-induced cardiotoxicity by reducing mitochondrial ROS levels, preserving normal mtDNA, and protecting mitochondrial function [26]. Cyclosporin A improves left ventricular function and isolated left ventricular muscle contraction in rat models by inhibiting mitochondrial permeability transition pore opening [27].

4.4 Cellular Apoptosis

DOX administration induces oxidative stress marker imbalances, stimulating intrinsic and extrinsic apoptotic pathways, leading to cardiomyocyte death. DOX-induced oxidative stress products activate heat shock factor-1 (HSF-1) and heat shock protein (HSP)-25, stimulating p53 protein production, a proapoptotic agent [28,29]. Different HSPs are activated post-DOX administration, affecting cardiomyocytes variably. HSP-25 and HSP-70 expression in mouse heart tissues induces inflammation, apoptosis, and fibrosis [30], while HSP-10, HSP-20, HSP-22, HSP-27, and HSP-60 exert antiapoptotic effects, protecting cardiomyocyte function [31].

4.5 Calcium Ion Homeostasis Disruption

DOX-induced cardiac damage also involves intracellular calcium (Ca^{2+}) homeostasis disruption [32]. In cardiomyocytes, Ca^{2+} is essential for myocardial excitation and contraction. DOX primarily increases intracellular Ca^{2+} concentrations by releasing calcium from the endoplasmic reticulum (ER) [33]. Calcium imbalance both results from and causes ROS formation; thus, Ca^{2+} chelators can inhibit DOX-mediated ROS activation and apoptosis. Magnesium sulfate significantly reverses DOX-induced QT interval prolongation by reducing intracellular Ca^{2+} through various mechanisms, including affecting sarcoplasmic reticulum Ca^{2+} pumps and altering sarcoplasmic Ca^{2+} pools [34].

4.6 Iron Ion Metabolism Dysregulation

Iron plays a crucial role in generating harmful free radicals that damage cardiac tissue. Numerous studies implicate metal ions in DOX-mediated cardiac injury. DOX interacts with metal ions, particularly iron, forming DOX-iron complexes [35,36]. Intracellular iron accumulation triggered by DOX

increases oxidative stress, a primary stage of DOX toxicity. Iron chelators effectively reduce DOX-induced cardiotoxicity [37]. Studies demonstrate that elevated body iron levels exacerbate DOX cardiotoxicity, with increased dietary iron worsening cardiac damage in rats. Iron chelators (e.g., desferrioxamine) exert cardioprotective effects against DOX-induced cardiotoxicity through the TGF-β1/Smad pathway [38]. DOX administration severely reduces red blood cell (RBC) counts and hemoglobin concentrations. Desferrioxamine protects cardiac and blood components from DOX toxicity, improving myocardial enzyme levels and RBC counts to normal ranges without significant myocardial damage in rat models [39]. Desferoxamine significantly reduces DOX-induced ECG and biochemical changes (e.g., malondialdehyde, glutathione, lactate dehydrogenase, creatine kinase-MB) [40]. Dexrazoxane, another iron chelator, binds intracellular free iron ions (Fe^{2+} and Fe^{3+}), removing iron from DOX complexes, thereby reducing hydroxyl radical and superoxide formation [41].

4.7 Gap Junction Dysfunction

Gap junctions, intercellular channel aggregates facilitating direct cell-cell communication and molecule/ion transport [41], mediate electrical connections between cardiomyocytes, maintaining normal cardiac rhythms. These junctions comprise membrane channels directly connecting adjacent cell cytoplasms, primarily composed of connexins. Connexin 43 (Cx43) is the most abundant connexin subtype in mammalian cardiomyocytes [42]. Cx43 expression and distribution changes are associated with myocardial diseases (e.g., hypertrophic cardiomyopathy, heart failure, ischemia) [43]. While typically located in gap junctions, Cx43 is also detected in mitochondria, where it exerts important cardioprotective effects. Under calcium overload and oxidative stress conditions, mitochondrial Cx43 plays critical roles in mitochondrial permeability [43,44]. DOX induces Cx43 expression and distribution changes, interfering with cardiomyocyte electrical signaling, intracellular calcium homeostasis, and mitochondrial function [45,46].

5. The Diagnosis of Anthracycline-Induced Cardiotoxicity

Electrocardiography (ECG) represents the most economical, simple, and convenient clinical diagnostic method. Anthracycline-induced cardiotoxicity may manifest as cardiac conduction system abnormalities, including nonspecific ST-T changes, QT interval prolongation, and other conduction abnormalities. However, ECG's specificity and accuracy in diagnosing cardiotoxicity are limited, as it reflects cardiac status at specific time points.

Echocardiography remains the first-line diagnostic tool for evaluating cardiac function in chemotherapy patients, with LVEF being the most commonly used assessment parameter. The ASE/EACVI consensus criteria for cancer treatment-related cardiac dysfunction are widely used for clinical diagnosis [47]. Global longitudinal strain (GLS) percentage changes show increasing potential as the strongest cardiotoxicity predictor [47-49]. Breast cancer clinical studies demonstrate GLS's 93% specificity and 91% negative predictive value for cardiotoxicity [48].

Serum biomarkers, including troponin, brain natriuretic peptide (BNP), and NT-proBNP, aid in early myocardial injury identification [50,51] in chemotherapy patients, offering the advantage of repeat testing within short intervals.

Myocardial biopsy remains the gold standard for myocardial injury evaluation but is invasive. Biomarkers provide noninvasive methods for early myocardial damage detection in chemotherapy patients.

MicroRNAs have emerged as early markers of chemotherapy-induced myocardial injury, detectable earlier than other biomarkers [52,53].

6. Clinical Prevention and Treatment of Anthracycline-Induced Cardiotoxicity

Chemotherapy represents a crucial breast cancer treatment modality, but associated cardiotoxicity poses significant challenges. Mitigating chemotherapy-induced cardiotoxicity maximizes clinical benefits. Pretreatment cardiovascular disease (CVD) risk assessment is recommended before initiating anthracycline therapy, including comprehensive history, physical examination, baseline LVEF assessment, and active management of preexisting CVD and/or cardiovascular risk factors throughout treatment [54]. Speckle-tracking echocardiography (STE)-derived GLS serves as a sensitive left ventricular systolic function marker, enabling early cardiotoxicity detection [49].

Existing anthracycline modifications provide opportunities for developing novel tumor-selective agents. A real-world study [55] involving 1,213 patients demonstrated similar efficacy but significantly reduced cardiotoxicity for both epirubicin and liposomal doxorubicin regimens. Co-encapsulating paclitaxel and doxorubicin in liposomes reduced cardiotoxicity compared to free drug combinations [56]. In HER2-positive breast cancer mouse models, H-ferritin doxorubicin and trastuzumab coadministration improved efficacy while reducing cardiotoxicity [57]. A trial [58] combining liposomal DOX, trastuzumab, and metformin as neoadjuvant therapy for HER2-positive breast cancer demonstrated favorable safety profiles.

Appropriate cardioprotective strategies are essential for preventing chemotherapy-associated cardiomyopathy. In typical heart failure, angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) lower blood pressure and attenuate cardiac remodeling. β-blockers reduce sympathetic activity, heart rate, and optimize excitation-contraction coupling. Consensus exists that ACEIs/ARBs and β-blockers (first-line HF therapy) should be initiated upon reduced ejection fraction HF diagnosis to reduce mortality and morbidity [59].

Dexrazoxane (DEX) remains the only FDA-approved drug for preventing anthracycline-induced cardiotoxicity [60]. Recent research focuses on developing more potent and applicable alternatives to DEX. Kollarova-Brazdova et al. [61] and Bavlovi Pisk et al. [62] identified GK-667, showing high cellular protection in rabbit models and neonatal ventricular cardiomyocytes (NVCMs). Bures et al. [63] developed JR-311, a novel DEX derivative demonstrating efficacy.

Other recent reports explore breast cancer cardiomyopathy prevention and treatment. Kang et al. [64] reviewed over 20 published studies and ongoing trials, concluding that exercise therapy effectively protects against and potentially reverses anthracycline-induced cardiotoxicity. As nonpharmacological strategy, exercise therapy may represent a viable cardioprotective approach for chemotherapy - associated cardiomyopathy. Stem cell-based cardiac regenerative therapy is extensively investigated for repairing and protecting chemotherapy-induced myocardial damage.

7. Conclusion and Future Perspectives

Anthracyclines significantly improve breast cancer patient survival but are associated with cardiovascular disease development. Chemotherapy-treated breast cancer patients often experience LVEF reduction, potentially progressing to left ventricular dysfunction or heart failure. Balancing cancer treatment benefits with patient-specific cardiovascular risks and identifying cardiotoxicity prevention strategies are essential for improving long-term outcomes and quality of life. Advances in imaging and circulating biomarkers facilitate early subclinical cardiotoxicity identification, enabling early intervention before clinical CVD progression. Growing awareness of cardiotoxic cancer treatment-associated cardiovascular system damage has fostered a new multidisciplinary approach to cardiac oncology care for breast cancer patients. The multifactorial mechanisms underlying DOX-induced cardiotoxicity remain incompletely understood, necessitating further research to inform novel therapeutic strategies for preventing and treating DOX-induced cardiotoxicity.

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